dominant disorders, NF1. Loss of the NF1 protein product, neurofibromin, is associated with benign neurofibromas, comprised largely of Schwann Cells (SC). The number and severity of neurofibromas increase during times of high hormonal activity, including puberty and pregnancy, and may regress after childbirth. Mouse embryonic stem cells (mESC) that are NF1 wild type, heterozygous, or null can be differentiated into SC-like cells, which express SC and myelination markers. Two human NF1 tumor cell lines, one from a benign plexiform neurofibroma and one from a malignant peripheral nerve sheath tumor (MPNST) cell line, have also been shown to become Schwann-like cells in culture. We have used this model system to study the proliferation of these SC-like cells expressing various levels of neurofibromin, to differing levels of the hormones that increase during pregnancy: progesterone (P4), estrogen (E2), or testosterone (T), with and without their respective receptor inhibitors (RU486, ICI182780, Flutamide). We have also found that an E2 metabolite, 2-Methoxyestradiol (2ME2), which has been found to kill many types of tumor cells, is cytotoxic to the NF1−/− malignant tumor cell line, while it inhibits proliferation in the other cell lines. 2ME2 could also provide a new treatment avenue for NF1 tumors sensitive to hormones at times of greatest hormonal influence on tumor growth.

doi:10.1016/j.ydbio.2006.04.085

69
Myelin transcription factor 1 is required for islet development and maintenance

Sui Wang, Jia Zhang, Aizhen Zhao, Guoqiang Gu
Vanderbilt University, Nashville, TN, USA

Vertebrate islet has four major cell types: α, β, δ and PP-cells, producing glucagon, insulin, somatostatin and pancreatic polypeptide, respectively. Myt1 transcription factor is specifically expressed in endocrine progenitors. Previous overexpression and gene knockdown results suggested that Myt1 is involved in endocrine islet differentiation. To verify these findings, we performed gene targeting to knock out Myt1. Global Myt1−/− mice die immediately after birth. Their pancreata do not exhibit prominent defects. Yet double immuno-labeling revealed abnormal co-expression of several hormones in islet cells in these mutants, suggesting that Myt1 is required for endocrine differentiation. In order to assess whether these early defects have any functional consequences, we generated pancreatic specific Myt1 mutants using a Cre–Lox-mediated gene inactivation approach. Intraperitoneal glucose tolerance tests showed that the pancreatic specific Myt1 knockout male mice were diabetic. Serum insulin secretion test further revealed an impairment of insulin secretion. Consistent with this diabetic phenotype, the expression level of Glut2, an important glucose sensor, was significantly reduced in the mutant pancreata. Because Myt1 expression is also detected in adult endocrine islets, we examined whether Myt1 function is required for adult islet function maintenance. We find that loss of Myt1 function in adult male mice results in diabetes. These findings suggested that Myt1 is required for both islet cell differentiation during embryogenesis and islet maintenance in adult mice.

doi:10.1016/j.ydbio.2006.04.086

70
Reduction of the Wnt inhibitor Dkk1 increases bone density in mice

Bryan T. MacDonald [1], Parul Sharma [2], Somying Patntirapong [2], Sivan M. Oyserman [3], Raymond E. Samuel [2], Xi He [1], A. Goldstein [3], Peter V. Hauschka [2]
[1] *Division of Neuroscience, Children's Hospital, Harvard Medical School, Boston, MA, USA*
[2] *Department of Orthopedic Surgery, Children's Hospital, Harvard Medical School, Boston, MA, USA*
[3] *Orthopaedic Research Laboratories, Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, MI, USA*

The Wnt/β-catenin signaling pathway has emerged as a key regulator in bone development and bone homeostasis. Loss-of-function mutations in the Wnt co-receptor Low-density lipoprotein receptor-related protein 5 (LRP5) result in osteoporosis and gain-of-function mutations in LRP5 result in high bone mass. Dickkopf-1 (Dkk1) is a secreted Wnt inhibitor that binds LRP5 and LRP6, reducing their availability to form a complex with Wnt and Frizzled. Therefore, it is expected that a decrease in Dkk1 will result in an increase in Wnt activity and a high bone mass phenotype. Dkk1−/− knockout mice are embryonic lethal, but by crossing null and hypomorphic Dkk1 alleles we are able to produce mice expressing low amounts of Dkk1 that survive to adulthood. In this study we have generated an allelic series of Dkk1 mutant mice to examine how reduced Dkk1 levels affect bone density. Using microCT imaging, we have scanned dissected femura and calvariae to analyze bone mineral density in trabecular and cortical regions. Our preliminary data suggest that Dkk1 mutant mice display a high bone mass phenotype that is inversely proportional to Dkk1 expression level. To ascertain the mechanism for this phenotype, we will isolate bone marrow stromal osteoblasts and osteoclasts from Dkk1 mutant mice and analyze their activity in cell culture.

doi:10.1016/j.ydbio.2006.04.087